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Supplementary file - video 0.5 speed.mp4	

Neurophysiological correlates of motor planning and movement initiation in ACL-reconstructed individuals: A case-control study

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Abstract

INTRODUCTION: Current evidence suggests that the loss of mechanoreceptors after anterior cruciate ligament (ACL) tears might be compensated by increased cortical motor planning. This occupation of cerebral resources may limit the potential to quickly adapt movements to unforeseen external stimuli in the athletic environment. To date, studies investigating such neural alterations during movement focused on simple, anticipated tasks with poor ecological validity. This trial, therefore, aims to investigate the cortical and biomechanical processes associated with sport- and injury-related movements in ACL-reconstructed individuals.

METHODS AND ANALYSIS: ACL-reconstructed participants and uninjured controls will perform repetitive counter-movement jumps with single-leg landings. Two different conditions are to be completed: anticipated (n = 35) vs. non-anticipated (n = 35) landings. Under the anticipated condition, participants receive the visual information depicting the requested landing leg prior to the jump. In the non-anticipated condition, this information will be provided about 400 ms prior to landing. Neural correlates of motor planning will be measured using electroencephalography. In detail, movement-related cortical potentials, frequency spectral power, and functional connectivity will be assessed. Biomechanical landing quality will be captured via a capacitive force plate. Calculated parameters encompass time to stabilization, vertical peak ground reaction force and center of pressure path length. Potential systematic differences between ACL-reconstructed individuals and controls will be identified in dependence of jumping condition (anticipated, non-anticipated, left and right landing leg and rest) by using interference statistics. In Potential associations between the cortical and biomechanical measures will be calculated by means of correlation analysis. In case of statistical significance ($\alpha < .05$.) further confounders (cofactors) will be considered.

ETHICS AND DISSEMINATION: The independent Ethics Committee of the University of Frankfurt (Faculty of Psychology and Sport Sciences) approved the study. Publications in peer-reviewed journals are planned. The findings will be presented at scientific conferences.

PROTOCOL REGISTRATION NUMBER: NCT03336060 (ClinicalTrials.gov)

Keywords: ACL rupture, neuromuscular function, cortical activity, neurocognition, neuroplasticity, central nervous system modifications

Article Summary

Strengths and limitations of this study

- First-time investigation of the link between electrocortical (EEG) activity (neural correlates of motor planning) and biomechanical function during typical sport- and injury-related movements (single-leg landings) in ACL-reconstructed individuals.
- Association between increased use of motor planning capacities and lower postural control during landing in ACL-reconstructed individuals may have major implications for rehabilitation and return to sports.
- Comparison against both, unaffected leg of the ACL-reconstructed individuals as well as uninjured controls and rigorous control of relevant confounders (e.g. higher and lower level cognitive functions).
- Investigator and participant blinding is not possible.

1. Introduction

Anterior cruciate ligament (ACL) tears represent the most frequent injury of the knee, particularly among young, physically active individuals[1, 2]. The disorder represents the leading cause of sports-related surgery[3] and, besides the severe acute and long-term consequences (e.g. pain, functional disability and impairements)[4], is associated with a higher lifetime risk of knee osteoarthritis[5]. Despite several multidisciplinary therapeutic approaches aiming to restore preinjury neuromuscular function, the odds of sustaining a second tear are significantly increased in afflicted individuals who returned to sports[6, 7]. It may be inferred that current rehabilitation paradigms fail to eliminate all impairments of the injury[8, 9].

The ACL rupture is, besides affecting mechanical stability, associated with substantial destructions of ligament mechanoreceptors[10]. These afferences, such as the Ruffini and Pacini corpuscles located in the ACL capable of providing proprioceptive information[11–13] regulate the activity of the Hamstring muscles[14–16]. As they represent a synergist of the ACL the Hamstrings are paramount

for functional stability of the knee joint[17, 18]. As the neural drive to the muscle depends on the sensory input, the above described peripheral deafferentation (mechanoreceptor damage), secondary to the rather acute consequences of the injury (e.g. pain, swelling and inflammation), even induce potentially neuroplastic changes in the brain[19, 20].

Current evidence suggests persistent central nervous system (CNS) adaptations occurring after ligamentous injuries and subsequent reconstruction surgeries[21]. Electroencephalographic (EEG) studies revealed increased activity of the frontal[22] and frontoparietal cortex[23] during the execution of sensorimotor tasks in ACL-reconstructed compared to unimpaired individuals. The authors conclude that this may be related to increased attentional control and somatosensory information processing related to a higher working memory load. Similarly, neuroimaging studies demonstrated ACL-injured individuals to exhibit a higher recruitment of cortical areas responsible for motor planning, sensory processing and visual-motor control during the execution of repetitive knee extensions[24, 25]. It may be concluded that the brain of ACL-injured and -reconstructed individuals relies more on higher-order motor control areas[26] and executive function even during simple, feedback-controlled movements, such as joint repositioning[23], force matching tasks[22] and knee extensions [8, 25] in order to compensate the reduced sensory input[21, 25, 27].

While the consequences of this supraspinal compensation strategy may be invisible during performing activities of daily living, they may place an athlete at risk of injury during sports and competition. To maintain neuromuscular control in a complex and dynamic athletic environment, a constant interaction between intrinsic (e.g. motor planning, joint position and movement) and extrinsic factors (e.g. other players, ball and non-anticipated stimuli) is required, based on the simultaneous integration and processing of varying proprioceptive, visual and vestibular information[8, 28–30]. In most situations leading to an injury, athletes are required to quickly adapt to the changing environment and cannot exclusively rely on pre-planned, anticipated movements[28, 29]. This, inter alia, refers to single-leg jump landings, which have been demonstrated to represent one of the major causes for non-contact knee injuries[31, 32].

To date, studies investigating the cortical alterations during movement of ACL patients focussed on simple, anticipated tasks mainly requiring feedback control and assesses in sitting or lying position[22–25]. Those tasks have poor ecological validity. Evidence is thus scarce regarding typical sport- and injury-related movements characterized by time constraints and feedforward control. The trial, therefore, aims to gain further insight into the cortical and biomechanical processes associated with non-anticipated/ unforeseen single-leg jump landings in ACL-reconstructed individuals and healthy controls. Specifically, the hypothesis will be tested that, in ACL-reconstructed individuals compared to unimpaired individuals, increased motor planning occurs occupying cerebral resources, which will no longer be available to ensure stable landings.

2. Methods

2.1 Study design and ethical standard

An explorative case-control study will be conducted. The trial will be carried out according to the Guidelines for Good Clinical Practice and according to the Declaration of Helsinki, including its modification of Fortaleza. Ethical approval has been obtained by the local committee of the university (Ethics Committee of the Faculty of Psychology and Sport Sciences, Goethe University Frankfurt, Germany, reference no: 2017/27) and all participants provide written informed consent. The study has been prospectively registered at clinicaltrials.gov (NCT03336060).

2.2 Study setup

After study enrollment, each individual will be scheduled for two visits within one week (Figure 1). At visit 1, potential confounders are assessed. Subsequently, participants will be familiarized with the anticipated and non-anticipated jump-landing tasks of the study. At visit 2, the main measurements are performed. Both visits will take place at comparable time of day.

Figure 1

2.3 Sample

Recruited participants will be ACL-reconstructed (cases) and healthy, uninjured individuals (controls). All participants will be recruited at local physical rehabilitation centres, physiotherapists and medical practices, sports clubs, fitness centres, and the local university's sports campus by means of flyers, e-mails and personal addressing. Inclusion criteria for all participants are (1) male sex, (2) age between 20 and 40 years, and (3) engagement in regular physical activity. Cases will be included if they have a history of unilateral, anterior cruciate ligament rupture with reconstruction surgery (> 1 year), irrespective of the replacement plastic and surgical access. The following exclusion criteria will be applied:

- exorbitant concomitant knee injury (i.e. bone bruise grad 3 or 4, full-thickness articular cartilage lesion larger than 1 cm^2, "unhappy triad") (cases)
- previous ACL-injury or surgery of the uninvolved knee (cases)
- life-quality impairing somatic/ psychological diseases/ disorders (all participants)
- acute or chronic inflammation of the musculoskeletal system / lower extremity (all participants)
- medication modifying pain perception and proprioception (all participants)
- muscle soreness (all participants)
- any severe musculoskeletal injury of the lower limb (controls)

2.4 Patient and Public Involvement

Patients will be not involved in this study: We only include ACL-reconstructed individuals (minimum one year after surgery) who have returned to their initial daily, physical and sportive activities and have restored their neuromuscular performance of the injured lower leg indicated by a side symmetry of single leg hop for distance testing above 85 percent.

2.5 Experimental approach

All participants will perform repetitive counter-movement jumps (hands placed at the hip) with single leg landings. Two different conditions are to be completed: anticipated vs. non-anticipated landings.

For the anticipated condition, the participants receive a visual information depicting the requested landing leg prior to the jump. In the non-anticipated condition, this information will be provided only after take-off. After a brief standardised warm-up (30 jumping jacks) and three test jumps, all participants have to perform a total of 70 successful jumps (n = 35 per condition, in randomized order), using the above described paradigm (for details, refer to Figure. 3 and 4).

The indication of the requested landing leg will be delivered by means of a laptop screen (17 inch diameter). It is positioned at 2.5 meters distance in front of the participants (Figure2). On the screen, a slide (Microsoft PowerPoint 2010) with a left or right footprint located on the left or right side of a vertical line is shown (Figure 2). In anticipated trials, the slide indicating the landing leg will be presented constantly before take-off (for details, refer to Figure 3). For the non-anticipated jumps, a single button USB switch (120 ms delay; KKmoon; South Africa) connected to the laptop will be used in order to elicit a slide change from the fixation cross to the landing leg slide upon take-off (for details, refer to Figure 4; supplementary file – Video).

Figure 2, 3, 4

A successful jump is defined as holding a stable landing position for at least 10 seconds. The participants will be allowed to use their arms to equilibrate the postural sway immediately after landing. After landing, their hands need to be re-positioned on the hip, while focussing a cross on the wall at eye level. Unsuccessful trials are categorised as landing errors (touching the ground with the free leg, leaving the force plate, touching the ground with the hands and falls) and/or task errors (landing on the wrong foot). To prevent excessive exhaustion during the experiment, the 70 jumps will be stratified into blocks of 10 with 5-minutes rests (sitting position) in between. Randomised selection of the jump conditions will be performed using BIAS for windows (University Frankfurt, Germany, Version 11.06).

Previous pilot testing revealed longer flight times for non-anticipated jump-landings compared to anticipated landings. Therefore, two strategies will be used to ensure uniform flight durations between the two disposed conditions. Firstly, during the familiarisation session, the participants will be trained

to constantly achieve comparable flight times of 480 to 520 milliseconds regardless of the jump condition. This duration, corresponding to a jumping height of about 30 cm, was chosen because the button switch has a latency of 120 ms from release to slide appearance and because other similar trials have used flight times of 400 ms[33, 34]. Secondly, in addition to the task familiarisation, during the breaks of the actual experiment, the participants will be provided with feedback regarding the achieved flight heights.

2.6 Measurements

Cortical measures of motor planning and preparation affordances serve as the main outcome of the trial. They were assessed prior to jumping. To ensure self-initiated movements the start of the jump is not triggered to an external stimulus in both jump-landing conditions. To reduce artefacts generated by eye movements, participants are asked to fixate the cross (Figure 3 and 4) shown on the laptop screen prior to jumping.

2.6.1 Cortical activity

Brain activity prior to jump movement initiation will be captured using a 32-channel electroencephalography (EEG) system with a wireless amplifier (LiveAmp, BrainProducts, Gilching, Germany). The device samples data at a frequency of 500 Hz (24-bit analog-to-digital) and has an integrated 3-axis acceleration sensor (measurement range: ± 2 g, Resolution: 1 mg/bit, 12 Bit; Error: ± 0.2 g). It is carried in a custom-made backpack, which is placed attached to the upper back of the participants. Positioning of the active slim electrodes embedded in the EEG cap (actiCAP, Easycap, Herrsching, Germany) will be performed according to the 10-20 international system. Impedance will be kept below 5 kΩ and no online filters will be applied.

The EEG signal will be recorded throughout the whole jump landing experiment. In addition, EEG data will be collected during 2-minute sitting rests prior to and after the 70 jumps. To reduce artefacts resulting from eye movement before and after the jump-landing experiments as well as during these measurements at rest, the participants will be instructed to fixate a cross, which is displayed on the laptop screen.

Three EEG parameters will be analysed: *Movement-related cortical potentials, frequency power spectra and functional connectivity*. The **Movement-related cortical potentials** (MRCP) occur about two seconds prior to voluntary movement and can be subdivided into successive three parts that will be assessed in the planned trial: *Bereitschaftspotential - negative slope - motor potential*[35, 36] (for a review see[37]). The *Bereitschaftspotential* is a slowly rising, bilateral negativity, generated in the supplementary and pre-supplementary motor area (1.5 to 0.5 seconds before movement onset; [38, 39]). Subsequently, a steeper negativity, the *negative slope* occurs and relates to the activity of the contralateral primary motor cortex (starting about 0.5 seconds prior to movement onset;[36, 40]). Both signals are followed by the *motor potential*[39], the peak negativity corresponding to the movement onset itself[41, 42]. MCRP are thought to reflect the motor cortical involvement during motor planning and preparing of a self-initiated movement[40]. For each of the MRCP measures, acceptable test-retest reliability has been reported [43].

To investigate the attentional and working memory processes needed for initiating and executing the jumps different **frequency power spectra** (Theta, Beta and Alpha) will be captured for frontal, central and parietal brain areas. Theta power will be measured in the frontal cortex and increases with higher levels of focused attention[44]. Alpha-2 power; inversely related to the activation[45] of the underlying somatosensory cortex, decreases with higher demands of sensory information-processing during sensorimotor tasks[23]. Both frontal Theta and parietal Alpha-2 have been shown to be strongly associated with working memory load[46]. It is, furthermore, well-known that the planning and preparation of voluntary movements are accompanied by an event-related desynchronization[47, 48] of the alpha and beta (including sensorimotor rhythm[49]) frequencies power corresponding to the cortical sensorimotor and parietal areas[50–54]. EEG power measures have been demonstrated to be highly reliable during both rest[55] and sensorimotor tasks[56].

Coherence analyses will be applied to examine the **functional connectivity** between the brain region specific co-working processes (motor planning areas, fronto-parietal network[46]). Following the approach of Sauseng et al.[46] and Silva et al.[57] coherence analysis will be conducted for the above mentioned frequency bands (e.g. Theta, Beta and Alpha). The test-retest-reliability of coherence testing has been shown to be sufficient to high for most brain areas and frequency bands[58].

2.6.2 Biomechanical parameters

A capacitive force measurement platform (50 Hz, Zebris FDM, Zebris Medical GmbH, Isny, Germany) will be used to assess postural stability following the single leg landings. Three parameters will be investigated *Time to stabilisation (TTS) - Vertical peak ground reaction force (GRF) - Center of pressure (COP) path length*: **Time to stabilisation (TTS)** describes the capacity to regain a stable stance as quickly as possible. It will be computed according to Colby et al.[59] and Wikstrom et al.[60]. Here, the dynamic cumulative average weight is calculated, based on the continuous force plate recordings until 10 seconds after landing. A stable stance is assumed as soon as the sequential average no longer exceeds the threshold of .25 standard deviations of the overall mean ground vertical force. The TTS has been demonstrated to exhibit moderate to high reliability[61]. **Vertical peak ground reaction force (GRF)** is the maximal vertical force impact upon landing. Using the raw data, the highest value [Newton] will be identified. **Center of pressure (COP) path length** represents the absolute cumulative sway of the total covered distance by the COP during the trial duration[62]. The path length will be assessed up until 2.5 seconds after the initial ground contact, which corresponds to the duration of the early dynamic landing phase[63]. In terms of balance assessment, COP measures have been demonstrated satisfactory reliability[64]. Intraindividually minima will be calculated for the both TTS, peak GRF, and COP path length in dependence of the disposed conditions.

2.6.3 Potential cofactors

The following parameters, potentially affecting the biomechanical and cortical outcomes, will be assessed:

- Dynamic stability feed-forward performance of the lower limb (Single leg hop for distance[65]).
- Postural control during single-leg stance (capacitive force measurement plate Zebris PDMS, Zebris, Isny, Germany)
- Limb alignment in frontal plane evaluated by using Single-Leg Landing Error Scoring System[66]

- Higher and lower level cognitive function (for details, see Table 1 and table 2)
- Level of arousal and alertness (10 cm VAS)
- Self-reported knee function (Lysholm Knee Score Scale;[67])
- Self-reported perceived fatigue of the lower limbs (10 cm VAS)
- Kinesiophobia, or fear of movement/ (re-)injury (Tampa Scale for Kinesiophobia;[68])
- Task-specific fear of movement/reinjury (10 cm VAS)
- Risk-taking behaviour (domain-specific risk-taking/ DOSPERT scale)

Table 1 gives an overview about the measures which are used to assess lower cognitive functions

Cognitive function	Measure	Format	Description	Primary Outcomes
Visuoperceptual abilities	Trail Making Test – A[69]	Pen/ paper	Link 25 disordered circles (number 1 to 25) in ascending order	Speed [s]
Reaction time/ speed of processing	Detection Task[70]	Computer-based*	Simple reaction time: attend to back side of playing card (screen), press predefined key when card turns to front side, 25 correct responses or max. 2 min.	Response time in correct responses [ms]
	Identification Task[70]	Computer-based*	Choice reaction time: attend to back side of playing card (screen), press one of two predefined keys according to colour (black or red) of front side of the turned card	Response time in correct responses [ms]

*Part of the neuropsychological, computerized test battery (CogState Ltd., Melbourne, Australia)

Table 2 gives an overview about the measures which are used to assess higher cognitive functions

Cognitive function	Measure	Format	Description	Primary Outcomes
Working memory	One back test[70]	Computer-based*	Attend to back side of playing card (screen), press one of two predefined keys, one key when turned card is same as immediately previous one, another key if not, 42 trials or max. 3 min.	Correct responses (% of total trials)
	Verbal digit span test[71]	Verbal	Forward condition: examiner read single digits, participant repeat in same order, 1 block of 2 different digit spans with same number of digits (start with 3 digits), one digit is added if one of both is repeated correctly (max. 8 digits); Backward condition: participant repeat readed digits in contrariwise order (start with 2, max. 7 digits)	Correct repeated digit spans [n]
Spatial working memory, learning efficiency	Groton Maze Learning Test [72]	Computer-based*	10 x 10 grid of squares (maze), start: top left corner, finish: bottom right corner (flag); goal: move to flag by clicking squares, if correct (green check mark appears), if not correct (red cross appears); 1 practice trial to learn pathway, 3 experimental trials in which the learned pathway has to repeated	Accuracy (total number of errors during three trials) and speed (time)
Visual memory	One card learning Test[70]	Computer-based*	Attend to back side of playing card (screen), cards turned in succession, press one predefined key if shown card has already appeared before, another key if not; 3 sequences (42 responses) or max. 3 min.	Accuracy (errors) and speed (time)
Cognitive flexibility	Tail Making Test – B[69]	Pen and paper	Link both disordered numbers (1–13) and letters (A–L) in alternating and ascending order (i.e., 1-A-2-B-3-C-4-D, etc.)	TMT difference = TMT-B [s] – TMT-A [s]
Response inhibition	Stop-Signal-Task[73]	Computer-based	Primary task: pressing one of two predefined keys according to two visual stimuli (75% of trials) Additional task: primary-task stimulus followed by tone (variable delay), indicating response to visual stimuli has to be avoided (stop-signal trials; 25% of the trials randomly selected).	mean stop signal reaction time [ms], accuracy of responses to no-signal trials (% of correct responses)
Response interference control	Stroop Colour-Word task[74]	Visual (sheet)	Familiarisation trials: read one sheet (3 columns) of words of colours (colour-words) printed in black ink (word reading; Stroop I), read colour-words printed in different colours (colour naming; Stroop II) Experimental trial: colour-words are printed in inconsistent colour ink (i.e. the word "green" is printed in blue ink), name the colour ink in which the colour-word is printed and not the word (i.e. the word "green" is printed in blue ink; interference; Stroop III).	Interference score = 'Stroop III – [(Stroop I + Stroop II) / 2]

*Part of the neuropsychological, computerized test battery (CogState Ltd., Melbourne, Australia)

2.7 EEG data processing

All EEG data will be filtered with a Butterworth high-pass filter of .001 Hz (24 dB/octave) and a low-pass filter of 40 Hz (24 dB/octave). For movement onset detection, the accelerometer data of the amplifier are used. In each jump trial, the EEG signals will be segmented into epochs of 2500 ms, from 2.000 ms before to 500 ms after movement onset. Components which are associated with eye movements and blinks will be removed by using Independent Component Analysis according to[75]. Trials with remaining artefacts will be rejected and only artefact-free trials will be used for analysis.

Time-domain specific analysis will be conducted to investigate the MRCP prior each jump. According to Spring et al.[41], MRCP will be divided into 3 successive epochs as follows: The Bereitschaftspotential divided in an early (BP-1: -1.500 to -1.000 ms) and late component (BP-2: -1.000 to -500 ms), and the negative slope component (-500 ms to 0 ms), including the motor potential. The mean and peak activity as well as onset time of the MRCP will be calculated primarily for the fronto-central (FC1, FC2) and central electrodes (C3, Cz, C4) as these channels correspond mainly to the supplementary and primary motor areas.

Frequency domain (spectral) analysis will be conducted by means of Fast Fourier Transformation dividing artefact-free epochs into the frequency power spectra for both measurement at rest (continuous EEG) and during the jump landing experiment. For the latter, in terms of time-frequency analysis, the 1.5 second EEG prior to movement onset will be separated into three successive 0.5 second epochs: -1.500 ms to -1.000 ms (T1), -1.000 s to -500 ms (T2) and -500 ms to 0 ms (T3). According to the literature, the mean frequency power will be mainly analysed for the frontal theta (Fz;[76]), central beta (C3, Cz, C4) and parietal alpha-2 (P3, Pz, P4). Finally, to examine functional connectivity, coherence analysis in the respective frequency bands will be applied[77]. All electrocortical outcomes will be calculated for each condition (anticipated/ non-anticipated, injured/non-injured leg). The EEG at rest measurements will be serve as control condition. All EEG data processing will be applied by using the BrainVision Analyzer software (Brain Products, Gilching, Germany)

2.7 Statistics

All calculations will be performed after checking the underlying assumptions for parametric or nonparametric testing (Shapiro-Wilk normality test for testing of normal distribution, Levene-test for variance homogeneity testing). The EEG outcome measures will be transformed to normalize distributions by using logarithmic based or arcsine transformation, if indicated. Data will be reported descriptively as means, standard deviations, and 95 % confidence intervals. Potential systematic differences between cases and controls (between-subject factors) and within both groups (within-subject factors) will be identified in dependence of jumping condition (anticipated, non-anticipated, left and right landing leg and rest) by using interference statistics. Potential associations between cortical activity measures and landing biomechanics will be calculated by using correlation analysis. If statistical associations occur, further confounders are introduced and considered by means of cofactor analysis. The level of statistical significance is set to $\alpha < .05$. Based on the exploratory nature of this study no alpha-error adjustment will be performed for multiple hypotheses testing. Microsoft Excel 2010 for Windows and SPSS Statistics (version 22.0, SPSS Inc., Chicago, IL, USA) will be used for statistical data analysis.

3. Discussion

To the best of our knowledge, the planned study is the first to explore both, the cortical and biomechanical fundamentals underlying non-anticipated single-leg landings in ACL-reconstructed individuals. Hence, this study will provide the first evidence concerning neural correlates of motor planning within sport- and injury-relevant movement paradigms.

Another strength of our design consists in the standardized assessment of relevant confounders potentially influencing the chosen outcomes. This, particularly, relates to higher and lower level cognitive functions, which have been identified to be associated with athletic performance (e.g. ball game sports[78, 79]) as well as knee injury risk[80] and incidence[81–83]

Our study will reveal results relevant for practice. If the hypothesized association between increased use of motor planning capacities and lower postural control during landing are verified, this would

have major implications for rehabilitation. Three key aspects may be of particular relevance: Above all (1), an increased reliance on motor planning during athletic high-risk situations could represent a new factor predisposing for ACL (re-)injury. Future prospective observational studies may therefore include non-anticipated jump-landing tasks in order to elucidate its value in predicting injury and monitoring the return to play / return to sports process.

Another issue (2) relates to the elaboration of new training approaches. In addition to physical exercise, e.g. dynamic balance, dual/-multi task training approaches (including external focus) and visual-motor exercise paradigms[8], electrophysiological methods, such as neuromuscular electrical stimulation[84], transcutaneous electrical nerve stimulation[85], electromyography biofeedback[86] and transcranial magnet stimulation[87] may represent intriguing options to restore somatosensory function and quadriceps corticomotor excitability of ACL-reconstructed individuals. Their application may open new therapeutic avenues, if changes in motor planning prior to non-anticipated jump landings could be evidenced in the cases.

Finally (3), affordable devices for daily practice would be needed to assess an individuals' ability to react and properly adjust his motor plan to an unforeseen/ non-anticipated external visual stimulus.

Despite the promising approach, some limitations have to be taken into account. No investigator nor participant blinding is possible using a quasi-experimental approach. Moreover, the neural correlates of motor planning are only detectable prior to the jump, but not after take-off due to serious EEG artefacts caused by the jump.

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Figure captions

Figure 1: Experimental study setup. The figure details the days in which participants are assessed.

Figure 2: Setup of the Jump-Landing Experiment.

Rubber mat (1); Hinge (2); Plastic panel (3); USB-button switch (4); Force plate (5); USB-cable connecting button switch with screen (PowerPoint; 6); Laptop with screen (17 Inch diameter; 7); Powerpoint-slides demonstrated on laptop screen indicating left or right foot landing (randomised order). Before each foot slide a separate slide containing a fixation cross is demonstrated (8).

Figure 3: Proceedings of anticipated jump-landings and the clarification when and how the visual stimulus indicating the side on which the single leg-landing has to be performed is presented.

A = slide with a fixation cross; B = slide is presented before the initiation of the jump. Participants start standing in bipedeal position on the plastic panel (3; Figure 2) while fixating the cross (A). The experimenter indicates the start of movement preparation by mentioning the condition "anticipated". Simultaneously the slide demonstrating the landing leg (B) is shown. Afterwards, participants initiate the jump by their own.

Figure 4: Proceedings of non-anticipated jump-landings and the clarification when and how the visual stimulus indicating the side on which the single leg-landing has to be performed is presented.

C = slide with a fixation cross (same as in A; Fig 3); D = USB-button (4, Figure 2) release during take-off (plastic panel elevates) initiating slide change; E = slide indicating the landing foot presented only after take-off Participants start standing in bipedeal position on the plastic panel (3; Figure 2) while fixating the cross (C). The experimenter mentions the jump-landing condition "non-anticipated". Afterwards, participants will initiate the jump by their own while C is still shown. The slide indicating the landing leg (E) appears about 120 milliseconds after take-off (button release; D) and is than shown continously (for more details, refer to the supplementary video file).

Supplementary video file

This video demonstrates in exemplary the non-anticipated jump-landing task according to the description provided in Figure 4.

Trial status

At the time of submission of this manuscript, recruitment is ongoing.

Abbreviations

ACL: Anterior cruciate ligament; COP: Center of Pressure; CNS: Central nervous system; EEG: Electroencephalography; GRF: Vertical peak ground reaction force; MRCP: Movement-related cortical potentials; TTS: Time to stabilisation; VAS: Visual analogue scale

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Conflict of interests

The authors have nothing to disclose.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. We declare that we have no competing interests.

Data statement

After completion of data acquisition the dataset will be available from ResearchGate.

Author Statement

FG developed the jump-landing setup and selected the neurophysiological and biomechanical outcome measures. FG wrote the first draft of the manuscript, revised the manuscript and provided final approval. TE assisted FG in the development of the trial jump-landing setup and in the selection of biomechanical outcome parameters. TE revised the manuscript, provided critical review and final approval. JW assisted FG in the development of the trial jump-landing setup and in the selection of biomechanical outcome parameters. JW revised the manuscript, provided critical review and final approval. DN revised the manuscript, provided critical review and final approval. JW assisted FG in the development of the trial jump-landing setup and in the selection of biomechanical outcome parameters. DN revised the manuscript, provided critical review and final approval. LV revised the manuscript and provided intellectual contributions to the final, submitted version of the manuscript. WB revised the manuscript and provided intellectual contributions to the final, submitted version of the manuscript. The material within has not been and will not be submitted for publication elsewhere except as an abstract. The authors agree that the copyright for our article is transferred to the publisher if and when the article is accepted for publication.

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Consent for publication

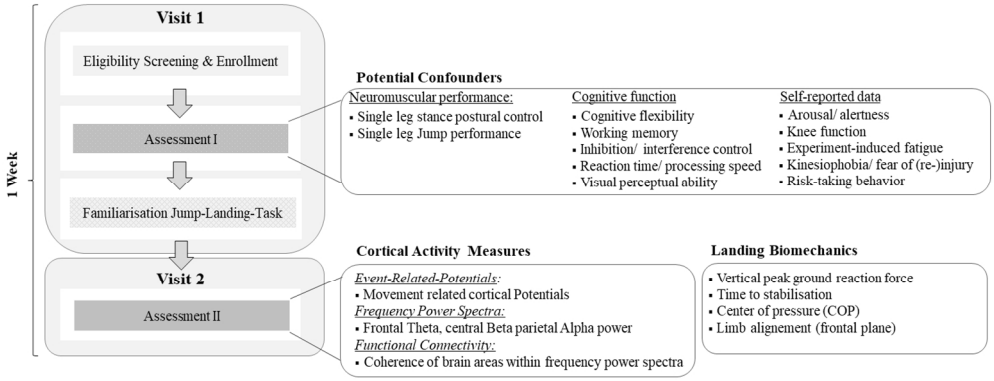
Written informed consent was obtained from the participants for publication of their individual details and accompanying images/ video in this manuscript. The consent form is held by the authors and is available for review by the Editor-in-Chief.

Ethics approval and consent to participate

The study was approved by the local Ethics Committee of the Faculty of Psychology and Sport Science, Goethe-University Frankfurt (reference number: 2017/27). The trial will be carried out according to the Guidelines for Good Clinical Practice and according to the Declaration of Helsinki, including its modification of Fortaleza. All participants provide informed consent prior to study enrollment.

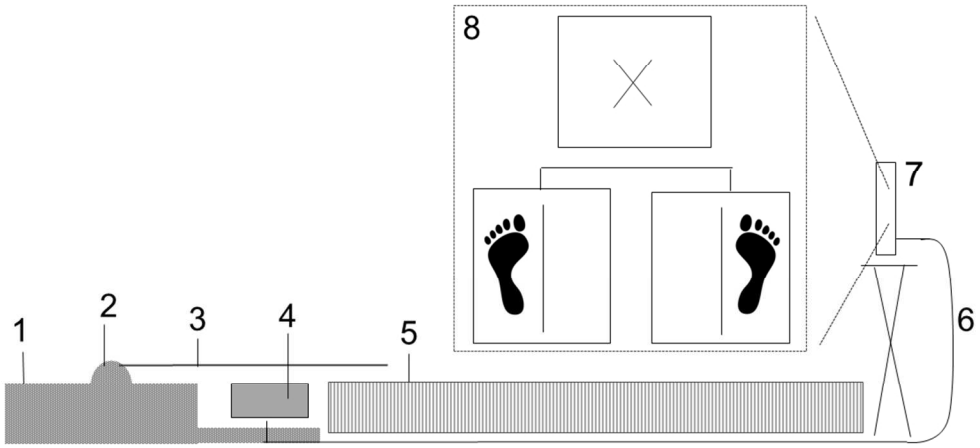
Trial registration

The study has been registered at clinicaltrials.gov (NCT03336060).



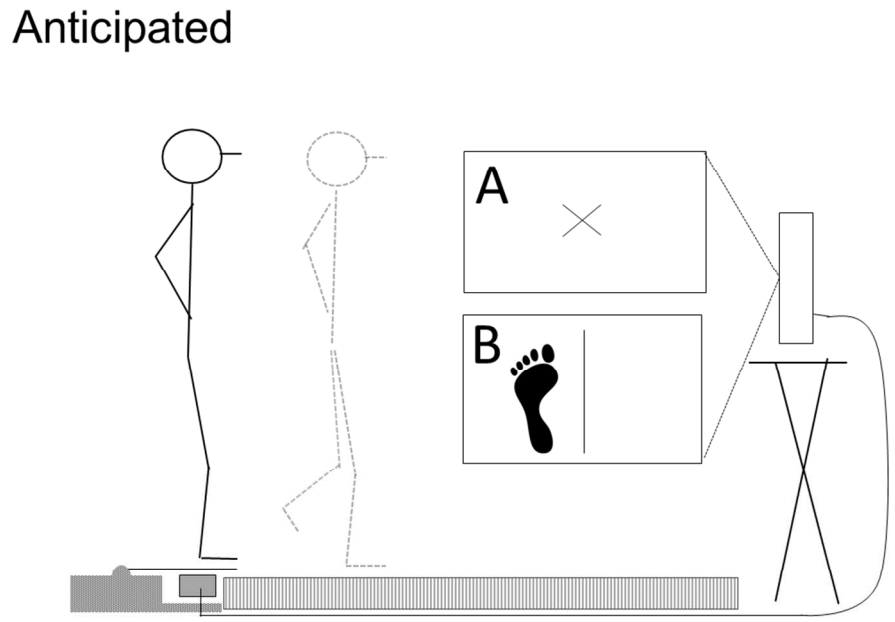
Experimental study setup. The figure details the days in which participants are assessed.

410x160mm (96 x 96 DPI)



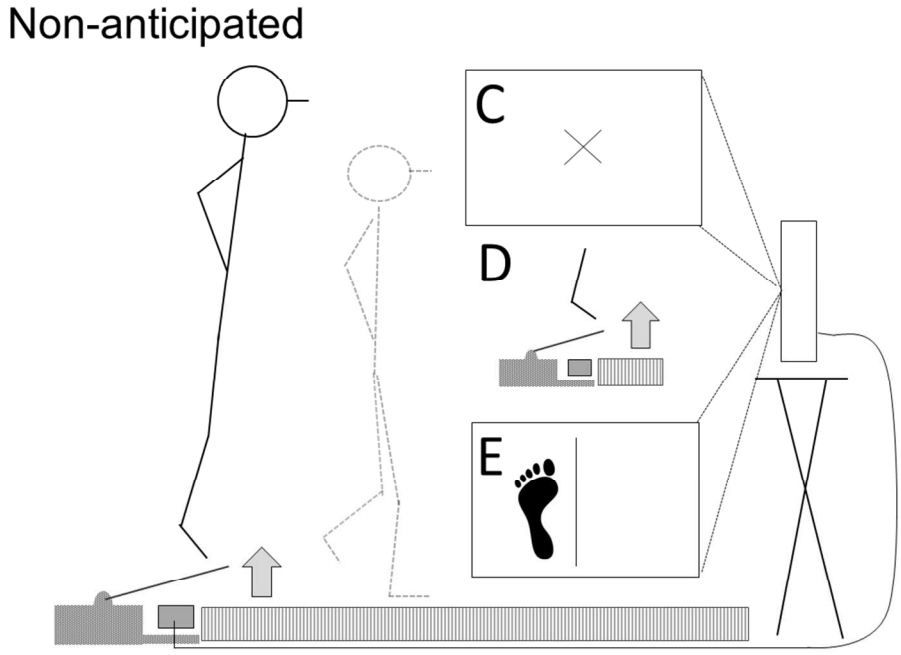
Setup of the Jump-Landing Experiment.

300x160mm (96 x 96 DPI)



Proceedings of anticipated jump-landings and the clarification when and how the visual stimulus indicating the side on which the single leg-landing has to be performed is presented.

300x210mm (96 x 96 DPI)



Proceedings of non-anticipated jump-landings and the clarification when and how the visual stimulus indicating the side on which the single leg-landing has to be performed is presented.

300x210mm (96 x 96 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *case-control studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	*(*a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	6,7
		(*b*) For matched studies, give matching criteria and the number of controls per case	n.a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7 f.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7 f.
Bias	9	Describe any efforts to address potential sources of bias	n.a.
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	12, 13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	13
		(*b*) Describe any methods used to examine subgroups and interactions	13
		(*c*) Explain how missing data were addressed	n.a.
		(*d*) If applicable, explain how matching of cases and controls was addressed	n.a.
		(*e*) Describe any sensitivity analyses	n.a.
Results			n.a. (study protocol)

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	"
		(b) Give reasons for non-participation at each stage	"
		(c) Consider use of a flow diagram	"
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	"
		(b) Indicate number of participants with missing data for each variable of interest	"
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	"
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	"
		(*b*) Report category boundaries when continuous variables were categorized	"
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	"
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	"
Discussion			13, 14
Key results	18	Summarise key results with reference to study objectives	n.a. (study protocol)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	"
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	"
Generalisability	21	Discuss the generalisability (external validity) of the study results	"
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Neurophysiological correlates of motor planning and movement initiation in ACL-reconstructed individuals: A case-control study

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Keywords:	ACL rupture, neuromuscular function, cortical activity, neurocognition, neuroplasticity, central nervous system modifications

Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.

Supplementary file - video 0.5 speed.mp4

Neurophysiological correlates of motor planning and movement initiation in ACL-reconstructed individuals: A case-control study

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Abstract

INTRODUCTION: Current evidence suggests that the loss of mechanoreceptors after anterior cruciate ligament (ACL) tears might be compensated by increased cortical motor planning. This occupation of cerebral resources may limit the potential to quickly adapt movements to unforeseen external stimuli in the athletic environment. To date, studies investigating such neural alterations during movement focused on simple, anticipated tasks with poor ecological validity. This trial, therefore, aims to investigate the cortical and biomechanical processes associated with more sport- and injury-related movements in ACL-reconstructed individuals.

METHODS AND ANALYSIS: ACL-reconstructed participants and uninjured controls will perform repetitive counter-movement jumps with single-leg landings. Two different conditions are to be completed: anticipated (n = 35) vs. unanticipated (n = 35) successful landings. Under the anticipated condition, participants receive the visual information depicting the requested landing leg prior to the jump. In the unanticipated condition, this information will be provided about ms prior to landing. Neural correlates of motor planning will be measured using electroencephalography. In detail, movement-related cortical potentials, frequency spectral power, and functional connectivity will be assessed. Biomechanical landing quality will be captured via a capacitive force plate. Calculated parameters encompass time to stabilization, vertical peak ground reaction force and center of pressure path length. Potential systematic differences between ACL-reconstructed individuals and controls will be identified in dependence of jumping condition (anticipated, unanticipated, left and right landing leg and rest) by using interference statistics. Potential associations between the cortical and biomechanical measures will be calculated by means of correlation analysis. In case of statistical significance ($\alpha <$ .05.) further confounders (cofactors) will be considered.

ETHICS AND DISSEMINATION: The independent Ethics Committee of the University of Frankfurt (Faculty of Psychology and Sport Sciences) approved the study. Publications in peer-reviewed journals are planned. The findings will be presented at scientific conferences.

PROTOCOL REGISTRATION NUMBER: NCT03336060 (ClinicalTrials.gov)

Keywords: ACL rupture, neuromuscular function, cortical activity, neurocognition, neuroplasticity, central nervous system modifications

Article Summary

Strengths and limitations of this study

- First-time investigation of the link between electrocortical (EEG) activity (neural correlates of motor planning) and biomechanical function during typical sport- and injury-related movements (single-leg landings) in ACL-reconstructed individuals.
- Association between increased use of motor planning capacities and lower postural control during landing in ACL-reconstructed individuals may have major implications for rehabilitation and return to sports.
- Comparison against both, unaffected leg of the ACL-reconstructed individuals as well as uninjured controls and rigorous control of relevant confounders (i.e. cognitive functions).
- Investigator and participant blinding is not possible.

1. Introduction

Anterior cruciate ligament (ACL) tears of the knee represent one of the most common sports-related injuries, particularly among young, physically active individuals[1, 2]. The disorder represents the leading cause of sports-related surgery[3] and, besides the severe acute and long-term consequences (e.g. pain, functional disability and impairements;[4]), is associated with a higher lifetime risk of knee osteoarthritis[5]. Despite several multidisciplinary therapeutic approaches aiming to restore preinjury neuromuscular function, the odds of sustaining a second tear are significantly increased in afflicted individuals who returned to sports[6, 7]. It may, therefore, be inferred that current rehabilitation paradigms fail to eliminate all impairments of the injury[8, 9].

Besides affecting mechanical stability, ACL rupture is associated with substantial destructions of ligament mechanoreceptors[10]. Under healthy conditions, the sensory receptors located in the ACL, e.g. Ruffini and Pacini corpuscles, provide essential proprioceptive information[11–13] and regulate the activity of the Hamstring muscles[14–16]. Representing a synergist of the ACL, the Hamstrings are paramount for functional stability of the knee joint[17, 18]. As the neural drive to the muscle depends on the sensory input, the above described peripheral deafferentation (mechanoreceptor

damage), secondary to the rather acute consequences of the injury (e.g. pain, swelling and inflammation), could induce neuroplastic changes in the brain[19, 20].

Current evidence demonstates persistent central nervous system (CNS) adaptations occurring after ligamentous injuries and subsequent reconstruction surgeries[21]. Electroencephalographic (EEG) studies revealed increased activity of the frontal [22] and frontoparietal cortex[23] during the execution of sensorimotor tasks in ACL-reconstructed compared to unimpaired controls. It has been suggested that this may be related to an increased attentional control and somatosensory information processing related to a higher working memory load[22, 23]. Similarly, neuroimaging studies showed ACL-injured individuals to exhibit a higher recruitment of cortical areas responsible for motor planning, sensory processing and visual-motor control during the execution of repetitive knee extensions[24, 25]. It may be concluded that the brain of ACL-injured and -reconstructed individuals relies more on higher-order motor control areas [26] and executive function even during simple, feedback-controlled movements, such as joint repositioning[23], force matching tasks[22] and knee extensions[8, 25] in order to compensate for the reduced sensory input[21, 25, 27].

While the consequences of this supraspinal compensation strategy may be invisible during activities of daily living, they may place an athlete at risk of injury during sports and competition. To maintain neuromuscular control in a complex and dynamic athletic environment, a constant interaction between intrinsic (e.g. motor planning, joint position and movement) and extrinsic factors (e.g. other players, ball and unanticipated stimuli) is required, based on the simultaneous integration and processing of varying proprioceptive, visual and vestibular information[8, 28–30]. In most situations leading to an injury, athletes, under high time constraints, are required to quickly adapt to the changing environment and cannot rely on pre-planned, anticipated movements exclusively[28, 29]. Against this background, current evidence suggests that rapid movement adaptations such as single-leg landings and cuttings in response to an unanticipated visual stimulus induce aberrant knee kinematics and kinetics that increase the risk of injury[31].

To date, studies investigating the cortical alterations during movement of ACL patients focussed on simple, anticipated tasks mainly requiring feedback control and assesses in sitting or lying

position[22–25]. Such tasks have poor ecological validity as they do not mimic sport-specific movement characteristics. Our planned trial, therefore, aims to gain further insight into the cortical and biomechanical processes associated with anticipated/ pre-planned vs. unanticipated/ unforeseen single-leg jump landings in ACL-reconstructed individuals and healthy controls. Specifically, the hypothesis will be tested that, ACL-reconstructed individuals compared to control individuals' exhibit increased cortical motor planning prior jumping. Furthermore, we assume that this higher use of cerebral resources will be associated with a lower landing quality in ACL reconstructed individuals.

2. Methods

2.1 Study design and ethical standard

An explorative case-control study will be conducted. The trial will be carried out according to the Guidelines for Good Clinical Practice and according to the Declaration of Helsinki, including its modification of Fortaleza. Ethical approval has been obtained by the local committee of the university (Ethics Committee of the Faculty of Psychology and Sport Sciences, Goethe University Frankfurt, Germany, reference no: 2017/27) and all participants provide written informed consent. The study has been prospectively registered at clinicaltrials.gov (NCT03336060).

2.2 Study setup

After study enrollment, each individual will be scheduled for two visits within one week (Figure 1). At visit 1, potential confounders (for details see 2.6.3) are assessed. Subsequently, participants will be familiarized with the anticipated and unanticipated jump-landing tasks of the study. At visit 2, the main measurements are performed. Both visits will take place at comparable time of day.

Figure 1

2.3 Sample

Recruited participants will be ACL-reconstructed (cases) and healthy, uninjured individuals (controls). All participants will be recruited at local physical rehabilitation centres, physiotherapists and medical

practices, sports clubs, fitness centres, and the local university's sports campus by means of flyers, e-mails and personal addressing. Inclusion criteria for all participants are (1) male sex, (2) age between 20 and 40 years, and (3) engagement in regular physical activity. Cases will be included if they have a history of unilateral, anterior cruciate ligament rupture with reconstruction surgery (> 1 year), irrespective of the graft used for reconstruction and surgical procedure, and full clearance to return to sport provided by the treated physician. The following exclusion criteria will be applied:

- exorbitant concomitant knee injury (i.e. bone bruise grad 3 or 4, full-thickness articular cartilage lesion larger than 1 cm^2, "unhappy triad") (cases)
- previous ACL-injury or surgery of the uninvolved knee (cases)
- life-quality impairing somatic/ psychological diseases/ disorders (all participants)
- acute or chronic inflammation/ disorders/ pain of the musculoskeletal system (all participants)
- medication modifying pain perception and proprioception (all participants)
- muscle soreness (all participants)
- any severe musculoskeletal injury of the lower limb (controls)
- history of head injuries (i.e. concussions)

2.4 Patient and Public Involvement

Patients will be not involved in this study: We only include ACL-reconstructed individuals (minimum one year after surgery) who have returned to their initial daily, physical and sportive activities and have restored their neuromuscular performance of the injured lower leg indicated by a side symmetry of single leg hop for distance testing above 85 percent. Achieving a ratio of at least 85% is recommended before return to unrestricted sport activities[32] as a lower limb asymmetry increases the risk for re-injury[33].

2.5 Experimental approach

All participants will perform repetitive counter-movement jumps (hands placed at the hip) with single leg landings. Two different conditions are to be completed: anticipated vs. unanticipated landings. For the anticipated condition, the participants receive a visual information depicting the requested landing

leg prior to the jump. In the unanticipated condition, this information will be provided only after take-off. After a brief standardised warm-up (30 jumping jacks) and three test jumps, all participants have to perform a total of 70 successful jumps (n = 35 per condition), using the above described paradigm. Pilot data indicated that a number of 35 successful trials per condition (5-minute breaks in sitting position after each 10 trials) are sufficient in order to produce stable results (neural correlates of motor planning; EEG) without evoking measurable exhaustion in any assessed parameter.

The indication of the requested landing leg will be delivered by means of a laptop screen (17 inch diameter). It is positioned at 2.5 meters distance in front of the participants (Figure2). On the screen, a slide (Microsoft PowerPoint 2010) with a left or right footprint located on the left or right side of a vertical line is shown (Figure 2).

Figure 2

In anticipated trials, the slide indicating the landing leg will be presented constantly before take-off (for details, refer to Figure 3).

Figure 3

For the unanticipated jumps, a single button USB switch (KKmoon; South Africa) connected to the laptop will be used in order to elicit a slide change (120 ms delay) from the fixation cross to the landing leg slide upon take-off (for details, refer to Figure 4; supplementary file – Video).

Figure 4

A successful jump is defined as holding a stable landing position for at least 10 seconds. The participants will be allowed to use their arms to equilibrate the postural sway immediately after landing. After landing, their hands need to be re-positioned on the hip, while focussing a cross on the wall at eye level. Unsuccessful trials are categorised as landing errors (touching the ground with the free leg, leaving the force plate, touching the ground with the hands and falls) and/or task errors (landing on the wrong foot). To prevent excessive exhaustion during the experiment, the 70 jumps will be stratified into blocks of 10 with 5-minutes rests (sitting position) in between. Randomised selection of the jump conditions will be performed using BIAS for windows (University Frankfurt, Germany, Version 11.06).

Previous pilot testing revealed longer flight times for unanticipated jump-landings compared to anticipated landings. Therefore, two strategies will be used to ensure uniform flight durations between the two disposed conditions. Firstly, during the familiarisation session, the participants will be trained to constantly achieve comparable flight times of 480 to 520 milliseconds regardless of the jump condition. This duration, corresponding to a jumping height of about 30 cm, was chosen because the button switch has a latency of 120 ms from release to slide appearance and because other similar trials have used flight times of 400 ms[34, 35]. Secondly, in addition to the task familiarisation, during the breaks of the actual experiment, the participants will be provided with feedback regarding the achieved flight heights. All participants are required to wear sports clothes (t-shirt and shorts) and indoor sports shoes during both task familiarisation session, and the actual jump landing experiment.

2.6 Measurements

Cortical measures of motor planning and preparation affordances serve as the main outcome of the trial. They were assessed prior to jumping. To ensure self-initiated movements the start of the jump is not triggered to an external stimulus in both jump-landing conditions. To reduce artefacts generated by eye movements, participants are asked to fixate the cross (Figure 3 and 4) shown on the laptop screen prior to jumping.

2.6.1 Cortical activity

Brain activity prior to jump movement initiation will be captured using a 32-channel electroencephalography (EEG) system with a wireless amplifier (LiveAmp, BrainProducts, Gilching, Germany). The device samples data at a frequency of 500 Hz (24-bit analog-to-digital) and has an integrated 3-axis acceleration sensor (measurement range: ± 2 g, Resolution: 1 mg/bit, 12 Bit; Error: ± 200 grams). It is carried in a custom-made backpack (700 grams), which is attached to the upper back of the participants. It is equipped with a power bank to guarantee permanent power supply of the amplifier (200 grams). Positioning of the active slim electrodes embedded in the EEG cap (actiCAP, Easycap, Herrsching, Germany) will be performed according to the 10-20 international system[36]. Impedance will be kept below 5 kΩ and no online filters will be applied.

The EEG signal will be recorded throughout the whole jump landing experiment. In addition, EEG data will be collected during 2-minute sitting rests prior to and after the 70 successful jumps. To reduce artefacts resulting from eye movements during these measurements, the participants will be instructed to fixate a cross, which is displayed on the laptop screen.

Three EEG parameters will be analysed: *Movement related cortical potentials, frequency power spectra and functional connectivity*. The **Movement-related cortical potentials** (MRCP) occur about two seconds prior to voluntary movement and can be subdivided into successive three parts that will be assessed in the planned trial: *Bereitschaftspotential - negative slope - motor potential* [37, 38] (for a review see[39]). The *Bereitschaftspotential* is a slowly rising, bilateral negativity, generated in the supplementary and pre-supplementary motor area (1.5 to 0.5 seconds before movement onset;[40, 41]). Subsequently, a steeper negativity, the *negative slope* occurs and relates to the activity of the contralateral primary motor cortex (starting about 0.5 seconds prior to movement onset;[38, 42]). Both signals are followed by the *motor potential*[41], the peak negativity corresponding to the movement onset itself[43, 44]. MCRP are thought to reflect the motor cortical involvement during motor planning and preparing of a self-initiated movement[42]. For each of the MRCP measures, acceptable test-retest reliability has been reported[45].

To investigate the attentional and working memory processes needed for initiating and executing the jumps different **frequency power spectra** (Theta, Beta and Alpha) will be captured for frontal, central and parietal brain areas. Theta power will be measured in the frontal cortex and increases with higher levels of focused attention[46]. Alpha-2 power; inversely related to the activation[47] of the underlying somatosensory cortex, decreases with higher demands of sensory information-processing during sensorimotor tasks[23]. Both frontal Theta and parietal Alpha-2 have been shown to be strongly associated with working memory load[48]. It is, furthermore, well-known that the planning and preparation of voluntary movements are accompanied by an event-related desynchronization[49, 50] of the alpha and beta (including sensorimotor rhythm[51]) frequencies power corresponding to the parietal and sensorimotor areas[52–56]. EEG power measures have been demonstrated to be highly reliable during both rest[57] and sensorimotor tasks[58].

Coherence analyses will be applied to examine the **functional connectivity** between the brain region specific co-working processes (motor planning areas; fronto-parietal network[48]). Following the approach of Sauseng et al.[48] and Silva et al.[59] coherence analysis will be conducted for the above mentioned frequency bands (e.g. Theta, Beta and Alpha). The test-retest-reliability of coherence testing has been shown to be sufficient to high for most brain areas and frequency bands[60].

2.6.2 Biomechanical parameters

A capacitive force measurement platform (50 Hz, Zebris FDM, Zebris Medical GmbH, Isny, Germany) will be used to assess postural stability following the single leg landings. Three parameters will be investigated: *Time to stabilisation (TTS) - Vertical peak ground reaction force (GRF) - Center of pressure (COP) path length*. **Time to stabilisation (TTS)** describes the capacity to regain a stable stance as quickly as possible. It will be computed according to Colby et al.[61] and Wikstrom et al.[62]. Here, the dynamic cumulative average weight is calculated, based on the continuous force plate recordings until 10 seconds after landing. A stable stance is assumed as soon as the sequential average no longer exceeds the threshold of .25 standard deviations of the overall mean ground vertical force. The TTS has been demonstrated to exhibit moderate to high reliability[63]. **Vertical peak ground reaction force (GRF)** is the maximal vertical force impact upon landing. Using the raw data, the highest value [Newton] will be identified. **Center of pressure (COP) path length** represents the absolute cumulative sway of the total covered distance by the COP during the trial duration[64]. The path length will be assessed up until 2.5 seconds after the initial ground contact, which corresponds to the duration of the early dynamic landing phase[65]. In terms of balance assessment, COP measures have been demonstrated satisfactory reliability[66]. Intra-individual mean values will be calculated for TTS, peak GRF, and COP path length in dependence of the disposed conditions.

2.6.3 Potential confounders

The following parameters, potentially affecting the biomechanical and cortical outcomes, will be assessed and analysed for their confounding influence:

- Dynamic stability feed-forward performance of the lower limb (Single leg hop for distance;[67]).

- Postural control during single-leg stance (capacitive force measurement plate Zebris PDMS, Zebris, Isny, Germany)
- Limb alignment in frontal plane evaluated by using Single-Leg Landing Error Scoring System[68]
- Cognitive function (Visuoperceptual abilities - Trail Making Test A[69]; Simple/ Choice reaction speed – Detection/ Identification Task[70]; Working memory – Verbal digit span test[71]; Spatial working memory/ learning efficiency – Groton Maze Learning Test[72]; Cognitive flexibility - Tail Making Test – B[69]; Response inhibition - Stop-Signal-Task[73]; Response interference control - Stroop Colour-Word task[74])
- Current and former physical/sports activities (i.e. primary sport, frequency/ duration per week, performance level, and years of experience)
- Self-reported knee function (Lysholm Knee Score Scale[75])
- Self-reported perceived fatigue of the lower limbs (10 cm VAS)
- Kinesiophobia, or fear of movement/ (re-)injury (Tampa Scale for Kinesiophobia[76])
- Task-specific fear of movement/reinjury (10 cm VAS)
- Level of arousal and alertness (10 cm VAS)
- Risk-taking behaviour (domain-specific risk-taking/ DOSPERT scale;[77])

2.7 EEG data processing

All EEG data will be filtered with a Butterworth high-pass filter of .001 Hz (24 dB/octave) and a low-pass filter of 40 Hz (24 dB/octave). For movement onset detection, the accelerometer data of the amplifier are used. In each jump trial, the EEG signals will be segmented into epochs of 2500 ms, from 2.000 ms before to 500 ms after movement onset. Components which are associated with eye movements and blinks will be removed by using Independent Component Analysis according to Winkler et al.[78]. Artefact removal will be applied according to the criteria used by Saliasi et al.[79] by using automated artefact rejection. Afterwards, all segments will be also visually inspected and trials with remaining artefacts (i.e. eye blinks, movement artefact) will be removed. Only artefact-free trials will be used for analysis.

Time-domain specific analysis will be conducted to investigate the MRCP prior each jump. According to Spring et al.[43], MRCP will be divided into 3 successive epochs as follows: The Bereitschaftspotential divided in an early (BP-1: -1.500 to -1.000 ms) and late component (BP-2: -1.000 to -500 ms), and the negative slope component (-500 ms to 0 ms), including the motor potential. The mean and peak activity as well as onset time of the MRCP will be calculated primarily for the fronto-central (FC1, FC2) and central electrodes (C3, Cz, C4) as these channels correspond mainly to the supplementary and primary motor areas.

Frequency domain (spectral) analysis will be conducted by means of Fast Fourier Transformation dividing artefact-free epochs into the frequency power spectra for both measurement at rest (continuous EEG) and during the jump landing experiment. For the latter, in terms of time-frequency analysis, the 1.5 second EEG prior to movement onset will be separated into three successive 0.5 second epochs: -1.500 ms to -1.000 ms (T1), -1.000 s to -500 ms (T2) and -500 ms to 0 ms (T3). According to the literature, the mean frequency power will be mainly analysed for the frontal theta (Fz;[80]), central beta (C3, Cz, C4) and parietal alpha-2 (P3, Pz, P4). Finally, to examine functional connectivity, coherence analysis in the respective frequency bands will be applied[81]. All electrocortical outcomes will be calculated for each condition (anticipated/ unanticipated, injured/uninjured leg). The EEG at rest measurements will be considered as control condition. All

EEG data processing will be applied by using the BrainVision Analyzer software (Brain Products, Gilching, Germany)

2.8 Statistics

All calculations will be performed after checking the underlying assumptions for parametric or nonparametric testing (Shapiro-Wilk normality test for testing of normal distribution, Levene-test for variance homogeneity testing). The EEG outcome measures will be transformed to normalize distributions by using logarithmic based or arcsine transformation, if indicated. Data will be reported descriptively as means, standard deviations, and 95 % confidence intervals. Potential systematic differences between cases and controls (between-subject factors) and within both groups (within-subject factors) will be identified in dependence of jumping condition (anticipated, unanticipated, left and right landing leg) by using interference statistics. The relationships between the cortical activity and biomechanical measures will be analysed by means of correlation analyses. The influence of the potential confounders on cortical and biomechanical outcomes during the jump landing task will be determined by correlation analysis, likewise. If statistical associations occur, significant confounders will be considered by means of cofactor analysis. To maintain homogeneity, participants of both groups will be matched based on age, jump performance, and their current physical/ sports activities (open- vs. closed skill sports[82].

The level of statistical significance is set to $\alpha < .05$. Based on the exploratory nature of this study no alpha-error adjustment will be performed for multiple hypotheses testing. Microsoft Excel 2010 for Windows and SPSS Statistics (version 24.0, SPSS Inc., Chicago, IL, USA) will be used for statistical data analysis.

3. Discussion

To the best of our knowledge, the planned study is the first to explore both, the cortical and biomechanical fundamentals underlying unanticipated single-leg landings in ACL-reconstructed individuals. Hence, this study will provide the first evidence concerning neural correlates of motor planning within sport- and injury-relevant movement paradigms.

Another strength of our design consists in the standardized assessment of relevant confounders potentially influencing the chosen outcomes. This, particularly, relates to cognitive functions, which have been identified to be associated with athletic performance (e.g. ball game sports[83, 84]) as well as knee injury risk[85] and incidence[86–88].

Our study will reveal results relevant for practice. If the hypothesized association between increased use of motor planning capacities and lower postural control during landing are verified, this would have major implications for rehabilitation. Three key aspects may be of particular relevance: Above all (1), an increased reliance on motor planning during athletic high-risk situations could represent a new factor predisposing for ACL (re-)injury. Future prospective observational studies may therefore include unanticipated jump-landing tasks in order to elucidate its value in predicting injury and monitoring the return to play / return to sports process.

Another issue (2) relates to the elaboration of new training approaches. In addition to physical exercise, e.g. dynamic balance, dual/-multi task training approaches (including external focus) and visual-motor exercise paradigms[8], electrophysiological methods, such as neuromuscular electrical stimulation[89], transcutaneous electrical nerve stimulation[90], electromyography biofeedback[91] and transcranial magnet stimulation[92] may represent intriguing options to restore somatosensory function and quadriceps corticomotor excitability of ACL-reconstructed individuals. Their application may open new therapeutic avenues, if changes in motor planning prior to unanticipated jump landings could be evidenced in the cases.

Finally (3), affordable devices for daily practice would be needed to assess an individuals' ability to react and properly adjust his motor plan to an unforeseen/ unanticipated external visual stimulus.

Despite the promising approach, some limitations have to be taken into account. No investigator nor participant blinding is possible using a quasi-experimental approach. Moreover, the neural correlates of motor planning are only detectable prior to the jump, but not after take-off due to serious EEG artefacts caused by the jump. Female athletes are at higher risk for non-contact ACL injuries compared to their male counterparts[93, 94]. To exclude the influences due to this variable only participants of one sex will be considered for inclusion. Males are chosen because pilot testing indicated that those were more likely to achieve the required jump height. The study results will refer to successful

landings only. However, unsuccessful trials (i.e. task errors) may provide additional information in terms of predicting injury risk. It could therefore be useful to investigate if cortical activities differ between successful and unsuccessful trials. This would certainly require a considerable increase of the total number of jump landings in order to obtain a sufficient amount of error trials for EEG analysis. Due to the considerably increased risk of fatigue and a greater effort for the participants resulting from this, adaptions to the described paradigm may be the second step and should be performed after proving the feasibility of the current approach.

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Figure captions

Figure 1: Experimental study setup. The figure details the days in which participants are assessed.

Figure 2: Setup of the Jump-Landing Experiment.

Rubber mat (1); Hinge (2); Plastic panel (3); USB-button switch (4); Force plate (5); USB-cable connecting button switch with screen (PowerPoint; 6); Laptop with screen (17 Inch diameter; 7); Powerpoint-slides demonstrated on laptop screen indicating left or right foot landing (randomised order). Before each foot slide a separate slide containing a fixation cross is demonstrated (8).

Figure 3: Proceedings of anticipated jump-landings and the clarification when and how the visual stimulus indicating the side on which the single leg-landing has to be performed is presented.

A = slide with a fixation cross; B = slide is presented before the initiation of the jump. Participants start standing in bipedeal position on the plastic panel (3; Figure 2) while fixating the cross (A). The experimenter indicates the start of movement preparation by mentioning the condition "anticipated". Simultaneously the slide demonstrating the landing leg (B) is shown. Afterwards, participants initiate the jump by their own.

Figure 4: Proceedings of unanticipated jump-landings and the clarification when and how the visual stimulus indicating the side on which the single leg-landing has to be performed is presented.

C = slide with a fixation cross (same as in A; Fig 3); D = USB-button (4, Figure 2) release during take-off (plastic panel elevates) initiating slide change; E = slide indicating the landing foot presented only after take-off. Participants start standing in bipedeal position on the plastic panel (3; Figure 2) while fixating the cross (C). The experimenter mentions the jump-landing condition "unanticipated". Afterwards, participants will initiate the jump by their own while C is still shown. The slide indicating the landing leg (E) appears about 120 milliseconds after take-off (button release; D) and is than shown continously (for more details, refer to the supplementary video file).

Supplementary video file

This video demonstrates in exemplary the unanticipated jump-landing task according to the description provided in Figure 4.

Trial status

At the time of submission of this manuscript, recruitment is ongoing.

Abbreviations

ACL: Anterior cruciate ligament; COP: Center of Pressure; CNS: Central nervous system; EEG: Electroencephalography; GRF: Vertical peak ground reaction force; MRCP: Movement-related cortical potentials; TTS: Time to stabilisation; VAS: Visual analogue scale

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Conflict of interests

The authors have nothing to disclose.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. We declare that we have no competing interests.

Data statement

After completion of data acquisition the dataset will be available from ResearchGate.

Author Statement

FG developed the jump-landing setup and selected the neurophysiological and biomechanical outcome measures. FG wrote the first draft of the manuscript, revised the manuscript and provided final approval. TE assisted FG in the development of the trial jump-landing setup and in the selection of biomechanical outcome parameters. TE revised the manuscript, provided critical review and final approval. JW assisted FG in the development of the trial jump-landing setup and in the selection of biomechanical outcome parameters. JW revised the manuscript, provided critical review and final approval. DN revised the manuscript, provided critical review and final approval. JW assisted FG in the development of the trial jump-landing setup and in the selection of biomechanical outcome parameters. DN revised the manuscript, provided critical review and final approval. LV revised the manuscript and provided intellectual contributions to the final, submitted version of the manuscript. WB revised the manuscript and provided intellectual contributions to the final, submitted version of the manuscript. The material within has not been and will not be submitted for publication elsewhere

except as an abstract. The authors agree that the copyright for our article is transferred to the publisher if and when the article is accepted for publication.

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Consent for publication

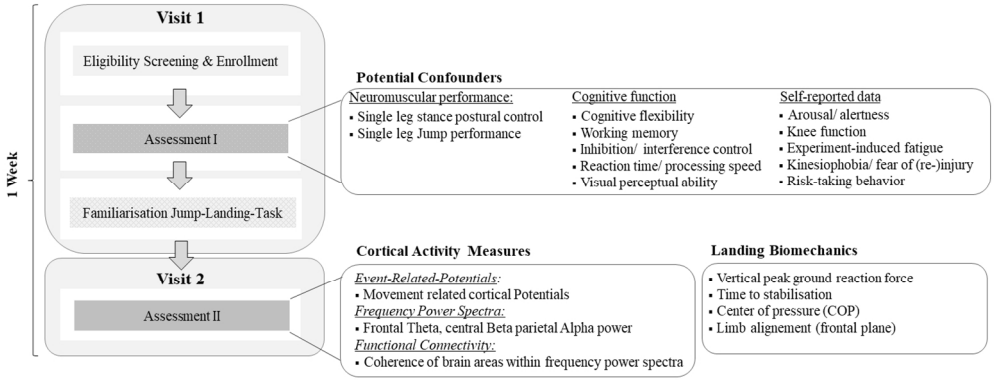
Written informed consent was obtained from the participants for publication of their individual details and accompanying images/ video in this manuscript. The consent form is held by the authors and is available for review by the Editor-in-Chief.

Ethics approval and consent to participate

The study was approved by the local Ethics Committee of the Faculty of Psychology and Sport Science, Goethe-University Frankfurt (reference number: 2017/27). The trial will be carried out according to the Guidelines for Good Clinical Practice and according to the Declaration of Helsinki, including its modification of Fortaleza. All participants provide informed consent prior to study enrollment.

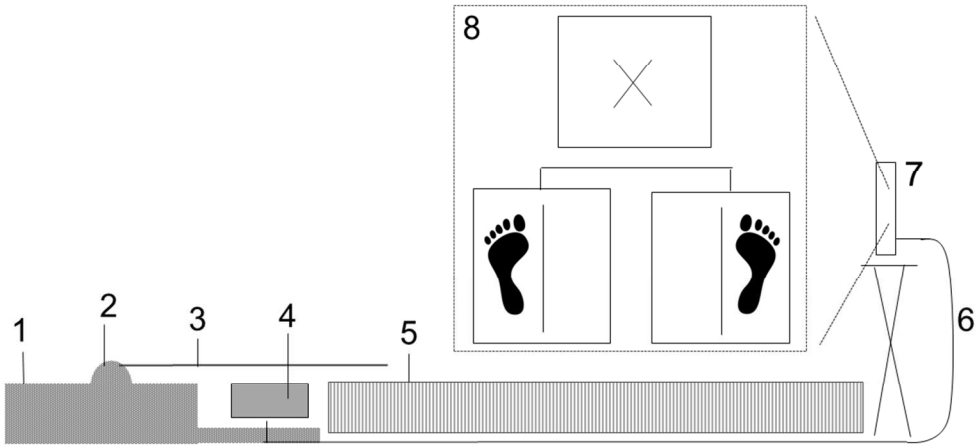
Trial registration

The study has been registered at clinicaltrials.gov (NCT03336060).



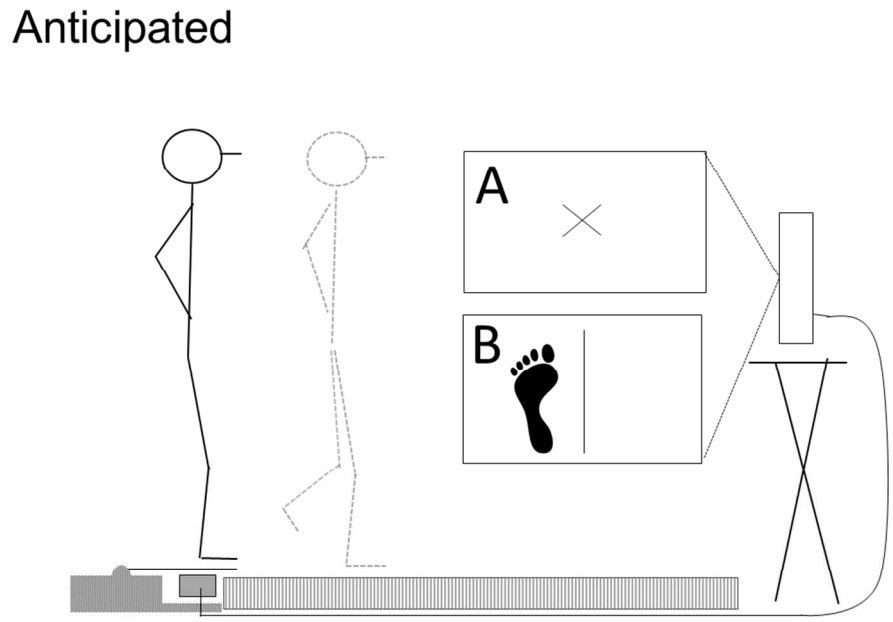
Experimental study setup. The figure details the days in which participants are assessed.

131x51mm (300 x 300 DPI)



Setup of the Jump-Landing Experiment.

96x51mm (300 x 300 DPI)



Proceedings of anticipated jump-landings and the clarification when and how the visual stimulus indicating the side on which the single leg-landing has to be performed is presented.

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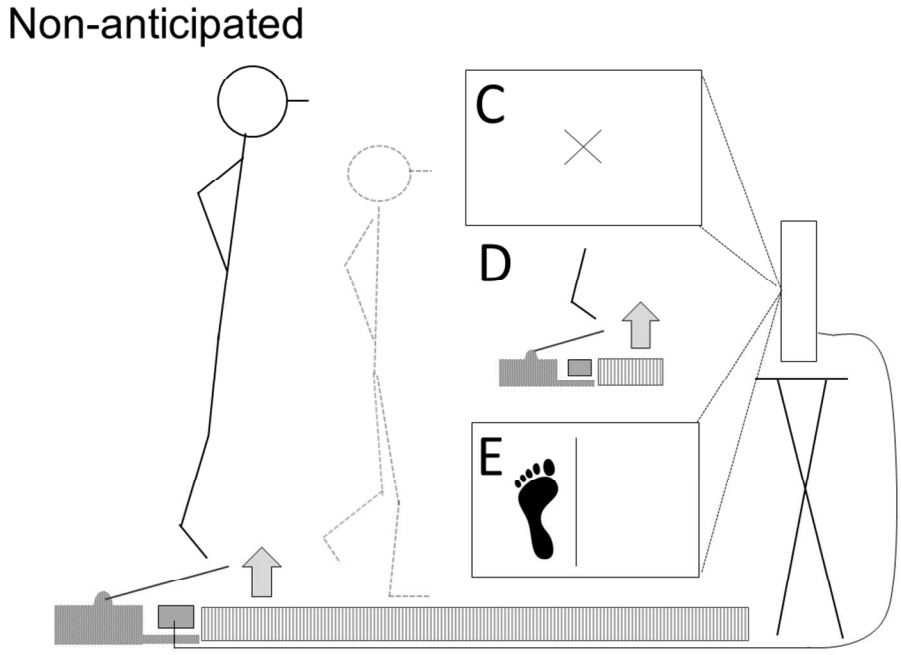

Proceedings of unanticipated jump-landings and the clarification when and how the visual stimulus indicating the side on which the single leg-landing has to be performed is presented.

96x67mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *case-control studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	*(*a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	6,7
		(*b*) For matched studies, give matching criteria and the number of controls per case	n.a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7 f.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7 f.
Bias	9	Describe any efforts to address potential sources of bias	n.a.
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	12, 13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	13
		(*b*) Describe any methods used to examine subgroups and interactions	13
		(*c*) Explain how missing data were addressed	n.a.
		(*d*) If applicable, explain how matching of cases and controls was addressed	n.a.
		(*e*) Describe any sensitivity analyses	n.a.
Results			n.a. (study protocol)

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	"
		(b) Give reasons for non-participation at each stage	"
		(c) Consider use of a flow diagram	"
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	"
		(b) Indicate number of participants with missing data for each variable of interest	"
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	"
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	"
		(*b*) Report category boundaries when continuous variables were categorized	"
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	"
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	"
Discussion			13, 14
Key results	18	Summarise key results with reference to study objectives	n.a. (study protocol)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	"
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	"
Generalisability	21	Discuss the generalisability (external validity) of the study results	"
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.